UNITED STAT DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/359,593	07/23/99	GARVER	R JHV-009.01

EXAMINER	
NGUYEN, D	
ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 10/03/01

025181
FOLEY, HOAG & ELIOT, LLP
PATENT GROUP
ONE POST OFFICE SQUARE
BOSTON MA 02109

HM12/1003

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev 11/00)

1- File Copy

Office Action Summary	Application No.	Applicant(s)
	09/359,593	GARVER ET AL
	Examiner	Art Unit
	Quang Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other.

DETAILED ACTION

Applicants' amendment filed on June 28, 2001 in Paper No. 15 has been entered. Claims 1-2 and 4-49 are pending in the present application.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 34, 39, 17-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons stated in the previous Office Action in Paper No. 10.

Claim 32 is directed to a method for delivering a nucleic acid into a cell comprising contacting a cell with a composition comprising a coacervate having limitations recited in claim 31, wherein the nucleic acid encodes a therapeutic agent, the cell is in a host and is transfected with the nucleic acid and express the therapeutic agent, and said agent produces a therapeutically beneficial response in said host. Claim 34 is directed to a method for delivering a nucleic acid into a cell in a host comprising contacting a cell with a composition comprising a coacervate having

limitations recited in claim 31, further comprising administering to said host said coacervate as a pharmaceutical composition. Claim 39 is directed to a method for preparing a pharmaceutical preparation, comprising combining a pharmaceutically acceptable excipient with a coacervate of cationic and anionic molecules, wherein a recombinant virus is encapsulated in said coacervate. Claims 17-20 and 22 are drawn to a composition of claim 15, wherein the microsphere when administered to a patient, provides controlled release of said expression vector.

The specification teaches the preparation of microspheres made by the coacervation of gelatin and alginate in the presence of recombinant adenovirus containing a luciferase expression cassette. It further revealed that the variation in the microsphere composition and the cross-linking modulates the amount and released pattern of recombinant virus in *in vitro* assays. Lyophilization of adenovirus within the microspheres was also shown to minimize the bioactive loss in comparison to the lyophilization of free adenovirus. With a human lung cancer engrafted on nude mouse model, it was demonstrated that bioactive adenovirus were released *in vivo* from the microspheres that were injected intratumorally, as evident by the luciferase activity in harvested tumor nodules. The above evidence has been noted and considered. However, the evidence can not be reasonably extrapolated to the instantly claimed invention because when read in light of the specification, it is drawn to methods for delivering a nucleic acid in the form of a coacervate to a cell in a host, and for preparing a pharmaceutical composition comprising a coacervate of the present invention for the purpose of gene therapy and/or nucleic acid immunization or for obtaining therapeutic

effects in general (See page 3 of the specification, lines 1-5 and 17-19). With respect to claims 17-20 and 22, the only purpose for administering the composition of claim 15 into a patient is intended for obtaining therapeutic effects. As enablement requires the specification to teach how to make and use the claimed invention, the instant specification fails to enable the make and use of the methods and compositions as claimed.

Regarding to the gene therapy aspect of the claims, the specification is not enabled for the claimed invention because it fails to provide guidance for one skilled in the art on how to make and use the claimed methods and compositions to obtain any therapeutic effect contemplated by Applicants to treat a plethora of diseases, disorders or genetic defects such as Duchenne and Becker muscular dystrophy, adenosine deaminase deficiency, cancer, Parkinson's, Alzheimer's, AIDS among many others (specification, pages 39-41). There is no specific guidance as to promoters, vectors or dosages that are utilized to treat a particular disease, disorder or a genetic defect. Moreover, there is no correlation between the luciferase activity detected in harvested tumor nodules that had been treated with coacervate microspheres containing recombinant adenoviruses of this invention with the therapeutic results expected for the treatment of aforementioned diseases, disorders and genetic defects. As the art does not teach such a correlation nor provide such guidance, it is incumbent upon the specification to do so. Additionally, at the effective filing date of the present application, gene therapy was still considered to be immature and highly unpredictable. Given the

lack of guidance or direction provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

As noted in the previous Office Actions that there are several factors limiting an effective gene therapy, and these include sub-optimal vectors, the lack of a stable *in vivo* transgene expression, and most importantly an efficient gene delivery to target cells or tissues. The specification fails to provide teachings showing that a gene construct in the coacervate microsphere of the instant invention could provide an efficient therapeutic transgene expression in targeted cells or tissues that results in desirable treatment outcomes for any and all diseases contemplated by the present application. Wivel and Wilson (cited in the previous Office Action) noted that an efficient gene therapy vector has not existed, and regarding the failure of the instant specification to provide guidance for a skilled artisan on how to make and use an efficient gene therapy vector other than those already known in the art, it would have required undue experimentation for one skilled in the art to practice the instant claimed invention.

The claims also encompass the utilization of a nucleic acid encoding any and all therapeutic agents to be incorporated in the coacervate microspheres to treat aforementioned diseases, disorders and genetic defects. However, the specification fails to address issues such as the fate of delivering recombinant gene transfer vectors, the fraction of vectors taken up by targeted cells once they are released from coacervate microspheres, the level of mRNA produced, the stability of the recombinant protein produced, the recombinant protein's compartmentalization and its bioactive

activity. These factors differ dramatically based on which recombinant protein being produced to treat which disease or disorder, and the desired therapeutic effect being sought. Therefore, the level of gene expression, its duration and its *in vivo* therapeutic effects are not always predictable, and hence they can not be overcome by routine experimentation. With the lack of guidance and direction provided by the specification, it would have required undue experimentation for a skilled artisan to make and use the instant invention.

Regarding to the deliverance of a transgene encoding a therapeutic agent to a target cell in a host via coacervate microspheres, the specification fails to provide sufficient guidance or teachings on vector targeting to specific tissues or cells in the subject. At the effective filing, vector targeting *in vivo* to desired cells, tissues or organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art

which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at about the time of the claimed invention resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). The specification fails to provide sufficient guidance for a skilled artisan on how to overcome the unpredictability of vector targeting *in vivo*, such that an efficient gene transfer and expression could be achieved in specific target cells via coacervate microspheres in order to attain the desired therapeutic results.

With regard to the nucleic acid immunization aspect of the instant claims, the state of the art is new and unpredictable at the effective filing date of the present application. Chattergoon et al. (FASEB J. 11:753-763, 1997) stated that "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology is considered an emerging technology" (column 1, paragraph 2, page 762) and "There is little evidence that the immune response induced by these vaccines will be completely protective against any human pathogen" (page 762, paragraph bridging

columns 1-2). Most recently, Leitner et al. (Vaccine 18:765-777, 2000) further stated that "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Leitner et al. also listed several variable factors affecting the immunogenicity of genetic vaccines. These include: the structure of the plasmid backbone, amount of plasmid delivered, expression levels of the antigen, age and strain of the particular species, target tissue, and route of immunization among others (See Table 1, page 767). It is also recognized that the animal model should correlate to the disease conditions studied. Furthermore, it is impossible to predict whether an untested antigen of an infectious pathogen will elicit a protective immune response in a given type of animal and the route of administration was recognized as being a critical parameter determining whether protective immunity is elicited. Since the instant claims encompass any and all hosts, one skilled in the art has also recognized that results observed in animal model system following testing of a DNA expression vector-based agent are not predictive of outcome or efficacy in applications in other species of animal or in humans, due to differences in anatomy, cell biology, genetics, and immunology between different types of animals and between the animal models and humans. This is further supported by the teachings of McCluskie et al. (Mol. Med. 5:287-300, 1999) who stated that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong

immune responses that had been seen in mice with the same vectors." (column 2, last paragraph, page 296). Against this background, the instant specification fails to provide any guidance demonstrating that the claimed methods of delivering a nucleic acid to a cell in a host via coacervate micropheres of the instant invention are effective for nucleic acid immunization purposes in any and all host for any and all diseases.

Additionally, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictablity of factors involved.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of gene therapy and nucleic acid immunization arts, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 28, 2001 in Paper No. 14 (pages 4-6) have been fully considered.

With respect to the issue of gene therapy and genetic immunization, Applicants argued that "At the time the application was filed, numerous clinical trials were ongoing in which DNA was introduced into subjects. Furthermore, many companies existed that had been formed to develop gene therapy techniques. Thus, even if some more experimentation may be necessary for developing certain gene therapy protocols, the evidence show that a person of skill in the art at the time the application was filed would have found gene therapy is credible". Examiner respectfully finds Applicants' argument to be unpersuasive because the above rejection is not made for the lack of utility, but rather for the lack of enablement.

Applicants further argued that "the specification and the general knowledge in the art at the time the invention was made provided sufficient teachings to enable a person of skill in the art to administer to a subject the claimed coacervates and obtain the desired results". Additionally, with respect to claims 17-20, Applicants argued that "Since the claims do not require a therapeutic effect, and since the specification provides *in vivo* uses which do not require a therapeutic effect (e.g., "imaging"), it is not necessary for Applicants to demonstrate that a therapeutic effect results from administration of the coacervate in the animal model".

Examiner respectfully finds Applicants' arguments are found to be unpersuasive because Applicants have not provided any factual evidence indicating that any of the

desired therapeutic effects contemplated by Applicants could be achieved. At the effective filing date of the present application, achieving therapeutic effects via gene therapy or genetic immunization is highly unpredictable as evidenced by the teachings of numerous articles cited above. With respect to claims 17-20 and 22, the only purpose for administering the composition of claim 15 into a patient is intended for obtaining therapeutic effects. Examiner can not imagine how a controlled release of an expression vector from the composition of claim 15 is required for imaging purpose as asserted by Applicants. It is further noted that the claims do not even recite any critical component required for the imaging purpose. Given the lack of guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Accordingly, claims 32, 34, 39 and 17-20 are rejected under 35 U.S.C. 112, first paragraph for the reasons set forth above.

Upon further consideration following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Claims 1-2, 4-10, 13-16, 21, 23-31, 33, 35, 40-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for controlled release of a nucleic acid comprising a coacervate encapsulates a nucleic acid associated with a delivery agent, wherein the coacevate comprises a polycation selected from the group consisting of gelatin and polylysine and a polyanion other than said nucleic acid; a gene delivery system or a kit comprising the

same, a method for preparing the same and a method for delivering a nucleic acid molecule into a cell using the same, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid; the same composition with various limitations recited in the dependent claims; a gene delivery system or a kit comprising the same and methods for preparing and using the same.

The instant specification is not enabled for the present broadly claimed invention for the following reasons. With respect to the broad claims drawn to a composition of the instant invention, as written it is unclear how the various recited components: (a) a coacervate, (b) a nucleic acid and (c) a delivery agent are structurally linked among themselves. Since the arrangement of the critical elements of the claimed composition is not clearly defined, it is uncertain whether any and all compositions having the recited components would function properly in releasing a nucleic acid molecule in a control and sustained manner for effectively delivering the nucleic acid into a cell. Apart from the teaching for the preparation of microspheres made by the coacervation of gelatin and alginate that encapsulates a recombinant adenovirus containing a luciferase expression cassette, the instant specification fails to provide sufficient guidance for a

skilled artisan on how to make and use the composition as broadly claimed without undue experimentation.

The instant claims encompass a composition or gene delivery system comprising a coacervate comprising any and all cationic molecule and any and all anionic molecule other than the nucleic acid, and methods of making and using the same. However, the state of the art at the effective filing date of the present application and the instant specification only teach that polycations such as albumin, collagen, elastin, gelatin and polyanions such as chondroitin sulfate, dermatan sulfate, hyaluronic acid, heparin may be used to form a coacervate microsphere or microcapsule (Leong et al., U.S. Patent No. 5,759,582, PTO-1449 # 6, AB; col. 4, lines 5-9; page 18, line 19 continues to line 10 of page 19 in this specification). Moreover, Leong et al. noted that the coarcevate formation to encapsulate a particular substance of interest can only be achieved by careful controlling the phrase separation conditions such as the choice and concentration of suitable polyelectrolytes, pH and temperature (col. 1, lines 60-67). Apart from a gelatin-alginate coacervate encapsulating a recombinant adenovirus exemplified in the present application and other gelatin-polyanion coacervates known in the art (Leong et al., U.S. Patent No. 5,759,582; Truong et al., U.S. Patent No. 6,025,337, Cited previously), the instant specification fails to provide sufficient guidance for one skilled in the art how to make and use a coacervate comprising a polycation other than gelatin, and that the coacervate is still capable of encapsulating and allowing a controlled release of a nucleic acid. Polylysine is the only alternative polycation that has a similar charge density to gelatin, and it is capable of complexing with nucleic acid

to form microparticles (Truong et al., U.S. Patent No. 6,025,337, col. 3, lines 27-34). It is also well known in the art that many polycations including polymer of cationic amino acid residues, e.g., polyarginine, histone, serum albumin are soluble or otherwise do not form particles that encapsulate the nucleic acids. As such, in the absence of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the composition, gene delivery system, a kit and methods of making and using the same as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-28, 30, 34, 35, 40-41, 43, 46 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and its dependent claims, as written it is unclear what is the structural relationship between component b) a nucleic acid and component c) a delivery agent in the claimed composition. Are these components structurally linked or do they interact in any manner in the composition? Or the components b) and c) are merely present in the claimed composition? Therefore, the metes and bounds of the claims can not be clearly

determined. Clarification is requested. Similarly, in claim 30 it is also unclear what is the structural relationship between the delivery agent and the nucleic acid contained in a transfer vector in the coacervate.

Amended claim 24 recites the limitation "said viral vector" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim and its dependent claims 25-28. There is no recitation of any viral vector in claims 1 and 2 from which claim 24 and its dependent claims are dependent upon.

Amended claim 32 recites the limitation "the cells" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Amended claim 34 recites the limitation "administering to said host" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any host in amended claim 31.

In claim 35, it is unclear what is encompassed by the phrase "instructions for using". Which instructions? The metes and bounds of the claim can not be clearly. determined.

In claims 40-41, 43 and 46, it is unclear what is the structural relationship between the delivery agent and the nucleic acid in the prepared gene delivery system as noted above. Suppose the delivery agent is not associated or encapsulated the nucleic acid, then how is the nucleic acid is delivered into cells? Clarification is requested.

Claim Rejections - 35 USC § 102

Claims 1-2, 10 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Russell-Jones et al. (U.S. Patent No. 6,159,502).

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid; the same composition wherein said coacervate is a microsphere or wherein said anionic molecule is alginate and a gene delivery system comprising the same.

With respect to the enabled scope of the instant claimed invention, Russell-Jones et al. disclose the preparation for complexes and compositions for oral delivery of a substance or substances to the circulation or lymphatic drainage system of a host. The complexes comprise a microparticle or microsphere coupled to at least one carrier, the carrier being capable of enabling the complex to be transported to the circulation or lymphatic drainage system via the mucosal epithelium of the host, and the microparticle or microsphere being capable of encapsulating the substances (See abstract). Specifically, Russell-Jones et al. teach that the microsphere can be made by complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims). Since a coacervate comprising a polyanion and a polylysine (also a delivery agent) that encapsulates a DNA or RNA or ribozyme taught by Russell-Jones meet every

limitations recited in the instant claims, the reference therefore anticipates the instant claimed invention.

Claim Rejections - 35 USC § 103

Claims 1-2, 4-5, 11-20, 23-31, 33-39 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997; Cited previously).

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid; the same composition with various limitations recited in dependent claims; a gene delivery system comprising the same, a kit containing the same gene delivery system and a method for delivering a nucleic acid into a cell using the same gene delivery system.

With respect to the composition claims 17-20, the intended use of the composition is not given any patentable weight in view of the prior art. With respect to claims 34 and 39, the pharmaceutical composition or preparation is interpreted as a composition or preparation containing a pharmaceutically acceptable excipient, and not for the intended pharmaceutical use. Within the enabled scope of the instant claimed invention, Russell-Jones et al. disclose the preparation for complexes and compositions for oral delivery of a substance or substances to the circulation or lymphatic drainage system of a host. The complexes comprise a microparticle or microsphere coupled to at

least one carrier, the carrier being capable of enabling the complex to be transported to the circulation or lymphatic drainage system via the mucosal epithelium of the host, and the microparticle or microsphere being capable of encapsulating the substances (See abstract). Specifically, Russell-Jones et al. teach that the microsphere can be made by complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims). Russell-Jones et al. also teach that the microspheres have size from 1 nanometer to 100 micrometers in diameters, and they can be prepared by a number of methods apart from the complex coacervation (col. 2 and col. 4, lines 39-42). Additionally, the disclosed complex or composition can be mixed with a pharmaceutically acceptable carrier, diluent, excipient and or adjuvant (col. 14, lines 7-14). Russell-Jones et al. also teach a method of orally delivering a substance, such as DNA, RNA or ribozymes to the circulation or lymphatic drainage system of a host by orally administering to the host the complex comprising the microsphere and wherein the substance is released from the microsphere when the complex enters the circulation or lymphatic drainage system of a host (See examples 13, 14 and the claims). Additionally, Russell-Jones et al. also disclose a kit comprising a plurality of different carriers and a plurality of different microparticles or microspheres containing the same or different substance of interest to prepare a complex for oral delivery (col. 6, lines 64-67). However, Russel-Jones et al. do not specifically teach the encapsulated DNA is in the form of a recombinant viral

vector, wherein the nucleic acid is a viral vector and the delivery agent is a virus of said viral vector.

Beer et al. disclosed a composition of poly (lactic-glycolic) acid (PLGA) microspheres containing a recombinant adenovirus, AdRSVntlacZ. Upon injection into the striatum of mice with microspheres containing AdRSVntlacZ, beta-galactosidase activity was detected in harvested brains after 7 days, and a dose dependent increase in beta-galactosidase activity was also noted (see Fig. 4). Although viable virus could be delivered both *in vitro* and *in vivo* from the PLGA microspheres, optimal microencapsulation yield, virus stability, and efficient transfer remained elusive (second column, second paragraph, page 63). Beer et al. suggested that different polymers should be investigated for their ability to allow for sustained release of recombinant viral vectors (column 2, last paragraph, page 63). It should be noted that beta-galactosidase is also an antigen upon administering into a host.

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to encapsulate the recombinant adenoviral virus into a microsphere composition taught by Russell-Jones et al. that is discussed above in light of the teachings of Beer et al. One of ordinary skilled in the art would have been motivated to carry out such modification to improve the microencapsulation yield and virus stability in the microspheres in order to improve the efficiency of gene delivery (Beer et al., page 63, column 2, first full paragraph). Beer et al. even suggested that other methods and different polymers should be investigated for their ability to allow sustained release of recombinant viral vectors (column 2, last paragraph, page 63). A

kit comprising the modified microsphere resulting from the combined teachings of Russell-Jones et al. and Beer et al. would have been obvious, as well as a method for delivering a nucleic acid to a cell using the modified microsphere. With respect to claim 16 reciting the incorporated virus comprising at least about five percent by weight of the microsphere, this would have been within the scope of skills of an ordinary artisan at the time of the instant invention to prepare the modified microsphere having such limitation. It is further noted that this is not the novel aspect of the present invention.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence to the contrary.

Claims 40-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997; Cited previously) as applied to claims 1-2, 4-5, 11-20, 23-31, 33, 35-38 and 48 above, and further in view of Leong et al. (U.S. Patent No. 5,759,582, PTO-1449 # 6, AB).

The claims are drawn to a method for preparing a gene delivery system in which the microspheres prepared from the coarcevation of a cationic molecule and an anionic molecule encapsulate a nucleic acid, preferably a recombinant virus, and a coacervate microsphere for transfection and expression of a recombinant protein prepared from the same method.

The teachings of Russell-Jones et al. and Beer et al. and the motivation for their combined teachings have been presented above. Neither reference specifically

discloses method steps for preparing the modified microsphere encapsulating a recombinant adenvirus resulting from the combined teachings of Russell-Jones et al. and Beer et al. Although Russell-Jones et al. teach that DNA or RNA or ribozyme can be encapsulated in a microsphere prepared by complex coacervation between mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose among others with polycations of polylysine and gelatin (col. 10, lines 16-22 and the claims), they also do not specifically disclose the method steps, presumably the process of forming a microsphere prepared from a complex coacervation is well known. At the effective filing date of the present application, Leong et al. (US Patent No. 5,759,582) taught a method for preparing a pharmaceutical composition in the form of a coacervate microsphere, comprising the following steps: (a) providing a gelatin (a cationic molecule) aqueous solution; (b) providing a chondroitin sulfate (an anionic molecule) aqueous solution; (c) adding a therapeutically effective amount of a pharmaceutically active substance either to the solution in step (a) or to the solution in step (b); (d) mixing the gelatin and chondroitin sulfate solutions to form a coacervate suspension; (e) adding a crosslinking agent to the coacervate suspension to crosslink the coacervates, the coacervates encapsulating the pharmaceutically active substance; and (f) incubating the coacervate suspension to form microspheres and recovering the microspheres. (col. 2 in summary of invention). Leong et al. further taught that after recovering the microspheres, they may be washed and dried in a standard techniques, e.g., lyophilization (col. 4, last paragraph).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method of preparing a coarcevate microsphere disclosed by Leong et al. (US Patent No. 5,759,582) in light of the combined teachings of Russell-Jones et al. and Beer et al., by substituting a pharmaceutical composition comprising water soluble protein, peptide, glycoprotein, or mixture thereof in step (c) with a recombinant adenovirus in order to obtain the modified microsphere that encapsulates a recombinant adenovirus. The motivations for one of ordinary skilled artisan tc carry out the above modification are already discussed in the rejection of claims 1-2, 4-5, 11-20, 23-31, 33, 35-38 and 48 above.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-6, 11-15, 17, 22 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO 94/23738, PTO-1449#6, AK).

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid; the same composition with various limitations recited in the dependent claims.

With respect to composition claims 17 and 22, the intended use of the composition is not given any patentable weight in view of the prior art. Within the

enabled scope of the instant claimed invention, Russell-Jones et al. disclose the preparation for complexes and compositions for oral delivery of a substance or substances to the circulation or lymphatic drainage system of a host. The complexes comprise a microparticle or microsphere coupled to at least one carrier, the carrier being capable of enabling the complex to be transported to the circulation or lymphatic drainage system via the mucosal epithelium of the host, and the microparticle or microsphere being capable of encapsulating the substances (See abstract). Specifically, Russell-Jones et al. teach that the microsphere can be made by complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims). However, Russell-Jones et al. do not specifically teach that the encapsulated DNA is in the form of a recombinant transfer vector, or the encapsulated DNA is associated with any delivery agent or that the disclosed microsphere comprises a second expression vector. At the effective filing date of the present application, McElligott et al. teach that DNA or RNA molecules can be conjugated by way of chemical bonds with promoting material which promotes the uptake or the transport to the nucleus of cells, such as fatty acids, phospholipids, glycolipids among others (Summary of the invention), and that the conjugated genetic material can be encapsulated in a microsphere suitable for the controlled release of the nucleic acid molecule to a target cell (Summary of the invention). The microsphere can be prepared by various methods available in the art

(pages 15-26). McElligott et al. further teach that encapsulation of genetic material would protect the nucleotides from enzymatic degradation before they are released, and that controlled release of genes would also reduce lethality to the host by allowing controlled expression of the product (page 4, lines 3-7). Specifically, McElligott et al. disclosed various plasmid expression vectors having a promoter, regulatory region along with the coding region of specific nucleotide sequence encoding for the desired gene product, including cytokines or gene product killing cancer cells (page 9, lines 20-24; page 28, col. 20-22 and examples 1, 5).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to incorporate DNA or RNA in the form of a plasmid expression vector conjugate as taught by McElligott et al. into the microsphere composition disclosed by Russell-Jones et al. One of ordinary skilled in the art would have been motivated to carry out the above modification, because the DNA in the form of a conjugate facilitates the uptake and integration of the genetic material into cells upon being released from the microsphere as taught by McElligott et al. With respect to claim 22 reciting further comprising a second expression vector, it would have been obvious and a matter of choice for an investigator to have two different expression vectors being encapsulated into the same microsphere.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 2 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO 94/23738, PTO-1449#6, AK) as applied to claims 1-6, 11-15, 17, 22 and 49 above, and further in view of Leong et al. (U.S. Patent No. 5,759,582, PTO-1449 # 6, AB) and Gombotz et al. (U.S. Patent No. 5,942,253).

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid; the same composition wherein said coacervate is a microsphere and wherein the microsphere is crosslinked by a crosslinking agent, preferably a metal cation and more preferably calcium.

The teachings of Russell-Jones et al. and McElligott et al. and the motivation for their combined teachings have been presented above. Neither reference specifically teach that the modified microsphere can be crosslinked by a crosslinking agent, preferably a metal ion and more preferably calcium ions. However, at the effective filing date of the present application, it is known that a coacervate microsphere can be crosslinked to reinforce the encapsulation of the active substance as taught by Leong et al. (col. 3, lines 63-65), and that glutaraldehyde can be used as a crosslinking agent for a coacervate of gelatin and chondrotin sulfate (col. 4, lines 17-19). Additionally, in teaching the preparation of a microsphere for a controlled and prolonged release of GM-CSF orally to a host, Gombotz et al. disclose that alginate in a hydrogel microsphere

can be ionically cross-linked with divalent ions such as calcium (col. 6, lines 14-22; col. 8, line 66 continues to line 6 of col. 9).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to crosslink the modified microsphere composition resulting from the combined teachings of Russell-Jones et al. and McElligott et al. with crosslinking agents such as glutaraldehyde or calcium ions (for coacervate involving alginate as a polyanion) in light of the teachings of Leong et al. and Gombotz et al. One of ordinary skilled in the art would have been motivated to carry out the above modification to reinforce the encapsulation of the bioactive substance, for this instance the conjugated-DNA complex, or the overall stability of the modified microsphere as taught by Leong et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

Claims 32, 34 and 39 are free of prior art. At the time of the instant invention, the prior art does not teach or fairly suggests claimed methods for delivering a nucleic acid encoding a therapeutic agent in cells of a host using the coacervate composition of the present invention and for preparing a pharmaceutical composition comprising the same coacervate composition as claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Dave

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER